F-XXXXXXXX

PRODUCT INFORMATION

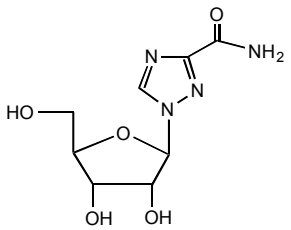
REBETOL® (ribavirin, USP) Capsules and Oral Solution

- **REBETOL monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. (See WARNINGS).**
- **The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with REBETOL therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with REBETOL. (See WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).**
- **Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days, and so it may persist in nonplasma compartments for as long as 6 months. Therefore, REBETOL therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking REBETOL therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS-Information for Patients and Pregnancy Category X).**

DESCRIPTION

REBETOL®

REBETOL is Schering Corporation's brand name for ribavirin, a nucleoside analog. The chemical name of ribavirin is 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide and has the following structural formula:



Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.

REBETOL Capsules consist of a white powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin, sodium lauryl sulfate, silicon dioxide, and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue #2 aluminum lake.

REBETOL Oral Solution is a clear, colorless to pale or light yellow bubble gum-flavored liquid. Each milliliter of the solution contains 40 mg of ribavirin and the inactive ingredients sucrose, glycerin, sorbitol, propylene glycol, sodium citrate, citric acid, sodium benzoate, natural and artificial flavor for bubble gum #15864, and water.

Mechanism of Action

The mechanism of inhibition of hepatitis C virus (HCV) RNA by combination therapy with ribavirin and interferon products has not been established.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Ribavirin Single- and multiple-dose pharmacokinetic properties in adults are summarized in **TABLE 1**. Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64% (44%). There was a linear relationship between dose and AUC_{tf} (AUC from time zero to last measurable concentration) following single doses of 200-1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400-600 mg.

Upon multiple oral dosing, based on $AUC12_{hr}$, a sixfold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 (37%) ng/mL. Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

Effect of Food on Absorption of Ribavirin Both AUC_{tf} and C_{max} increased by 70% when REBETOL Capsules were administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study. There are insufficient data to address the clinical relevance of these results. Clinical efficacy studies with REBETOL/INTRON A were conducted without instructions with respect to food consumption. During clinical studies with REBETOL/PEG-INTRON, all subjects were instructed to take REBETOL Capsules with food. (See **DOSAGE AND ADMINISTRATION**.)

Effect of Antacid on Absorption of Ribavirin Coadministration of REBETOL Capsules with an antacid containing magnesium, aluminum, and simethicone (Mylanta®[1]) resulted in a 14%

decrease in mean ribavirin AUC_{tf}. The clinical relevance of results from this single-dose study is unknown.

TABLE 1. Mean (% CV) Pharmacokinetic Parameters for REBETOL When Administered Individually to Adults

Parameter	REBETOL		
	Single Dose 600 mg Oral Solution (N=14)	Single Dose 600 mg Capsules (N=12)	Multiple Dose 600 mg BID Capsules (N=12)
T_{max} (hr)	1.00(34)	1.7 (46) ***	3 (60)
C_{max} *	872 (42)	782 (37)	3680 (85)
AUC_{tf} **	14098 (38)	13400 (48)	228000 (25)
$T_{1/2}$ (hr)		43.6 (47)	298 (30)
Apparent Volume of Distribution (L)		2825 (9) †	
Apparent Clearance (L/hr)		38.2 (40)	
Absolute Bioavailability		64% (44) ††	

* ng/mL
** ng.hr/mL
*** N = 11
† data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N = 5
†† N = 6

Ribavirin transport into nonplasma compartments has been most extensively studied in red blood cells, and has been identified to be primarily via an e_s-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the extensive volume of distribution. Ribavirin does not bind to plasma proteins.

Ribavirin has two pathways of metabolism: (i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of ^{14}C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P450 enzyme- mediated metabolism of ribavirin, with minimal potential for P450 enzyme-based drug interactions.

No pharmacokinetic interactions were noted between INTRON A Injection and REBETOL Capsules in a multiple-dose pharmacokinetic study.

Drug Interactions
Ribavirin has been shown *in vitro* to inhibit phosphorylation of zidovudine and stavudine which could lead to decreased antiretroviral activity. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities (see **PRECAUTIONS: Drug Interactions**).

1. Trademark of Johnson & Johnson-Merck Consumer Pharmaceuticals Co.

Special Populations

Renal Dysfunction The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to non HCV-infected subjects with varying degrees of renal dysfunction. The mean AUC_{tf} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90 mL/min). In subjects with creatinine clearance values between 30 to 60 mL/min, AUC_{tf} was twofold greater when compared to control subjects. The increased AUC_{tf} appears to be due to reduction of renal and non-renal clearance in these patients. Phase III efficacy trials included subjects with creatinine clearance values > 50 mL/min. The multiple dose pharmacokinetics of ribavirin cannot be accurately predicted in patients with renal dysfunction. Ribavirin is not effectively removed by hemodialysis. Patients with creatinine clearance <50 mL/min should not be treated with REBETOL (See **WARNINGS**).

Hepatic Dysfunction The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean AUC_{tf} values were not significantly different in subjects with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C) when compared to control subjects. However, the mean C_{max} values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects.
Elderly Patients Pharmacokinetic evaluations in elderly subjects have not been performed.
Gender There were no clinically significant pharmacokinetic differences noted in a single-dose study of eighteen male and eighteen female subjects.

Pediatric Patients Multiple-dose pharmacokinetic properties for REBETOL Capsules and INTRON A in pediatric patients with chronic hepatitis C between 5 and 16 years of age are summarized in TABLE 2. The pharmacokinetics of REBETOL and INTRON A (dose-normalized) are similar in adults and pediatric patients.
Complete pharmacokinetic characteristics of REBETOL Oral Solution have not been determined in pediatric patients. Ribavirin Cmin values were similar following administration of REBETOL Oral Solution or REBETOL Capsules during 48 weeks of therapy in pediatric patients (3 to 16 years of age).

Table 2 Mean (% CV) Multiple-Dose Pharmacokinetic Parameters for INTRON A and REBETOL Capsules When Administered to Pediatric Patients With Chronic Hepatitis C

Parameter	REBETOL 15mg/ kg/ day as 2 divided doses (n=17)	INTRON A 3MIU/m^2 TIW (n=54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/ml)	3275 (25)	51(48)
AUC*	29774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	ND

*AUC_{12} (ng.hr/ml) for REBETOL; AUC_{0-24} (IU.hr/ml) for INTRON A
ND=not done

*** *In this section of the label, numbers in parenthesis indicate % coefficient of variation.***

INDICATIONS AND USAGE

REBETOL (ribavirin, USP) Capsules and Oral Solution are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease previously untreated with alpha interferon or in patients 18 years of age and older who have relapsed following alpha interferon therapy.

REBETOL Capsules are indicated in combination with PEG-INTRON (peginterferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.

The safety and efficacy of REBETOL Capsules or Oral Solution with interferons other than INTRON A or PEG-INTRON products have not been established.

Pediatric Use
Evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load, should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the safety findings observed (see **PRECAUTIONS Pediatric Use**) for pediatric subjects in the clinical trials.

Description of Clinical Studies

REBETOL/INTRON A Combination Therapy

Adult Patients
Previously Untreated Patients
Adults with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research- based RT-PCR assay) who were previously untreated with alpha interferon therapy were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive REBETOL Capsules 1200 mg/day (1000 mg/day for patients

weighing ≤75 kg) plus INTRON A Injection 3 MIU TIW or INTRON A Injection plus placebo for 24 or 48 weeks followed by 24 weeks of off-therapy follow-up. The International study did not contain a 24- week INTRON A plus placebo treatment arm. The US study enrolled 912 patients who, at baseline, were 67% male, 89% Caucasian with a mean Knodell HAI score (I+II+III) of 7.5, and 72% genotype 1. The International study, conducted in Europe, Israel, Canada, and Australia, enrolled 799 patients (65% male, 95% Caucasian, mean Knodell score 6.8, and 58% genotype 1).
Study results are summarized in **TABLE 3**.

TABLE 3. Virologic and Histologic Responses: Previously Untreated Patients*

	US Study				International Study		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus REBETOL (N=265)	INTRON A plus REBETOL (N=268)	INTRON A plus Placebo (N=266)
Virologic Response							
-Responder[1]	65 (29)	13 (6)	85 (37)	27 (12)	86 (32)	113 (42)	46 (17)
- Nonresponder	147 (64)	194 (84)	110 (48)	168 (75)	158 (60)	120 (45)	196 (74)
-Missing Data	16 (7)	24 (10)	33 (14)	30 (13)	21 (8)	35 (13)	24 (9)
Histologic Response							
- Improvement[2]	102 (45)	77 (33)	96 (42)	65 (29)	103 (39)	102 (38)	69 (26)
-No improvement	77 (34)	99 (43)	61 (27)	93 (41)	85 (32)	58 (22)	111 (41)
-Missing Data	49 (21)	55 (24)	71 (31)	67 (30)	77 (29)	108 (40)	86 (32)

* Number (%) of patients.

1. Defined as HCV RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.

2. Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of $\geq$2 points.

Of patients who had not achieved HCV RNA below the limit of detection of the research based assay by week 24 of REBETOL/INTRON A treatment, less than 5% responded to an additional 24 weeks of combination treatment.

Among patients with HCV Genotype 1 treated with REBETOL/INTRON A therapy who achieved HCV RNA below the detection limit of the research- based assay by 24 weeks, those randomized to 48 weeks of treatment had higher virologic responses compared to those in the 24 week treatment group. There was no observed increase in response rates for patients with HCV nongenotype 1 randomized to REBETOL/INTRON A therapy for 48 weeks compared to 24 weeks.

Relapse Patients

Patients with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research- based RT-PCR assay) who had relapsed following one or two courses of interferon therapy (defined as abnormal serum ALT levels) were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive REBETOL 1200 mg/day (1000 mg/day for patients weighing ≤75 kg) plus INTRON A 3 MIU TIW or INTRON A plus placebo for 24 weeks followed by 24 weeks of off-therapy follow-up. The US study enrolled 153 patients who, at baseline, were 67% male, 92% Caucasian with a mean Knodell HAI score (I+II+III) of 6.8, and 58% genotype 1. The International study, conducted in Europe, Israel, Canada, and Australia, enrolled 192 patients (64% male, 95% Caucasian, mean Knodell score 6.6, and 56% genotype 1).

Study results are summarized in **TABLE 4**.

TABLE 4. Virologic and Histologic Responses: Relapse Patients*

	US Study		International Study	
	INTRON A plus REBETOL N=77	**INTRON A plus Placebo N=76**	**INTRON A plus REBETOL N=96**	**INTRON A plus Placebo N=96**
Virologic Response				
-Responder[1]	33 (43)	3 (4)	46 (48)	5 (5)
-Nonresponder	36 (47)	66 (87)	45 (47)	91 (95)
-Missing Data	8 (10)	7 (9)	5 (5)	0 (0)
Histologic Response				
-Improvement[2]	38 (49)	27 (36)	49 (51)	30 (31)
-No improvement	23 (30)	37 (49)	29 (30)	44 (46)
-Missing Data	16 (21)	12 (16)	18 (19)	22 (23)

* Number (%) of Patients.
1. Defined as HCV RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.
2. Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of $\geq$2 points.

Virologic and histologic responses were similar among male and female patients in both the previously untreated and relapse studies.

Pediatric Patients

Pediatric patients 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research-based RT-PCR assay) were treated with REBETOL 15 mg/kg per day plus INTRON A 3 MIU/m^2 TIW for 48 weeks followed by 24 weeks of off-therapy follow-up. A total of 118 patients received treatment who were 57% male, 80% Caucasian, and 78% genotype 1. Patients <5 years of age received REBETOL Oral Solution and those ≥5 years of age received either REBETOL Oral Solution or Capsules.

Study results are summarized in Table 5.

Table 5: Virologic Response: Previously Untreated Pediatric Patients *

	INTRON A 3 MIU/m^2 TIW Plus REBETOL 15 mg/kg/day
Overall Response[1] (n=118)	54 (46)
Genotype 1 (n=92)	33 (36)
Genotype non-1 (n=26)	21 (81)

*Number (%) of patients
1. Defined as HCV RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.

Patients with viral genotype 1, regardless of viral load, had a lower response rate to INTRON A/REBETOL combination therapy compared to patients with genotype non-1, 36% versus 81%. Patients with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 26% (13/50).

REBETOL/PEG-INTRON Combination Therapy

A randomized study compared treatment with two PEG-INTRON/REBETOL regimens [PEG-INTRON 1.5 µg/kg SC once weekly (QW)/REBETOL 800 mg PO daily (in divided doses); PEG-INTRON 1.5 µg/kg SC QW for 4 weeks then 0.5 µg/kg SC QW for 44 weeks/REBETOL 1000/1200 mg PO daily (in divided doses)] with INTRON A [3 MIU SC thrice weekly (TIW)/REBETOL 1000/1200 mg PO daily (in divided doses)] in 1530 adults with chronic hepatitis C. Interferon naïve patients were treated for 48 weeks and followed for 24 weeks post-treatment. Eligible patients had compensated liver disease, detectable HCV RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis.

Response to treatment was defined as undetectable HCV RNA at 24 weeks posttreatment (See **Table 6**).

Table 6 Rates of Response to Combination Treatment

	PEG-INTRON 1.5µg/kg QW REBETOL 800 mg QD	INTRON A 3 MIU TIW REBETOL 1000/1200mg QD
Overall [1,2] response	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2-6	75%(123/163)	73% (119/162)

[1]Serum HCV RNA was measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.

[2] Difference in overall treatment response (PEG-INTRON/REBETOL vs. INTRON A/REBETOL) is 6% with 95% confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline.

The response rate to PEG-INTRON 1.5→0.5µg/kg/REBETOL was essentially the same as the response to INTRON A/REBETOL (data not shown).

Patients with viral genotype 1, regardless of viral load, had a lower response rate to PEG-INTRON (1.5 μg/kg)/REBETOL combination therapy compared to patients with other viral genotypes. Patients with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 30% (78/256) compared to a response rate of 29% (71/247) with INTRON A/REBETOL combination therapy.

Patients with lower body weight tended to have higher adverse event rates (see **ADVERSE REACTIONS**) and higher response rates than patients with higher body weights. Differences in response rates between treatment arms did not substantially vary with body weight.

Treatment response rates with PEG-INTRON/REBETOL combination therapy were 49% in men and 56% in women. Response rates were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians the number of non-Caucasians studied (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors.

Liver biopsies were obtained before and after treatment in 68% of patients. Compared to baseline approximately 2/3 of patients in all treatment groups were observed to have a modest reduction in inflammation.

CONTRAINDICATIONS

Pregnancy
REBETOL Capsules and Oral Solution may cause birth defects and/or death of the exposed fetus. REBETOL therapy is contraindicated for use in women who are pregnant or in men whose female partners are pregnant. (See **WARNINGS, PRECAUTIONS-Information for Patients and Pregnancy Category X**).

REBETOL Capsules and Oral Solution are contraindicated in patients with a history of hypersensitivity to ribavirin or any component of the capsule.

Patients with autoimmune hepatitis must not be treated with combination REBETOL/INTRON A therapy because using these medicines can make the hepatitis worse.

Patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia) should not be treated with REBETOL Capsules or Oral Solution.

WARNINGS

Based on results of clinical trials ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection; therefore, REBETOL Capsules or Oral Solution must not be used alone. The safety and efficacy of REBETOL Capsules and Oral Solution have

only been established when used together with INTRON A (interferon alfa-2b, recombinant) as REBETRON Combination Therapy or with PEG-INTRON Injection.

There are significant adverse events caused by REBETOL/INTRON A or PEG-INTRON therapy, including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up. The REBETRON Combination Therapy and PEG-INTRON package inserts should be reviewed in their entirety prior to initiation of combination treatment for additional safety information.

Pregnancy
REBETOL Capsules and Oral Solution may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. REBETOL has demonstrated significant teratogenic and/or embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin. REBETOL THERAPY SHOULD NOT BE STARTED UNTIL A REPORT OF A NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED IMMEDIATELY PRIOR TO PLANNED INITIATION OF THERAPY. Patients should be instructed to use at least two forms of effective contraception during treatment and during the six month period after treatment has been stopped based on multiple dose half-life of ribavirin of 12 days. Pregnancy testing should occur monthly during REBETOL therapy and for six months after therapy has stopped (see CONTRAINDICATIONS and PRECAUTIONS: Information for Patients and Pregnancy Category X).

Anemia
The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 10% of REBETOL/INTRON A-treated patients in clinical trials (See adverse reactions laboratory values - *hemoglobin*). The anemia associated with REBETOL capsules occurs within 1 - 2 weeks of initiation of therapy. BECAUSE THE INITIAL DROP IN HEMOGLOBIN MAY BE SIGNIFICANT, IT IS ADVISED THAT HEMOGLOBIN OR HEMATOCRIT BE OBTAINED PRETREATMENT AND AT WEEK 2 AND WEEK 4 OF THERAPY, OR MORE FREQUENTLY IF CLINICALLY INDICATED. Patients should then be followed as clinically appropriate.

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by REBETOL. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. (See DOSAGE AND ADMINISTRATION: Guidelines for Dose Modification.) Because cardiac disease may be worsened by drug induced anemia,

patients with a history of significant or unstable cardiac disease should not use REBETOL. (See ADVERSE REACTIONS.)

REBETOL and INTRON A or PEG-INTRON therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.

REBETOL should not be used in patients with creatinine clearance <50 mL/min. (**See Clinical Pharmacology, Special populations.**)

Pulmonary
Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis and pneumonia, have been reported during therapy with REBETOL/INTRON A; occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, the patient should be closely monitored, and if appropriate, combination REBETOL/INTRON A treatment should be discontinued.

PRECAUTIONS

The safety and efficacy of REBETOL/INTRON A and PEG-INTRON therapy for the treatment of HIV infection, adenovirus, RSV, parainfluenza, or influenza infections have not been established. REBETOL Capsules should not be used for these indications. Ribavirin for inhalation has a separate package insert, which should be consulted if ribavirin inhalation therapy is being considered.

The safety and efficacy of REBETOL/INTRON A therapy has not been established in liver or other organ transplant patients, patients with decompensated liver disease due to hepatitis C infection, patients who are nonresponders to interferon therapy, or patients coinfected with HBV or HIV.

Information for Patients
Patients must be informed that REBETOL Capsules and Oral Solution may cause birth defects and/or death of the exposed fetus. REBETOL must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking REBETOL. REBETOL should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Patients must perform a pregnancy test monthly during therapy and for 6 months posttherapy. Women of childbearing potential must be counseled about use of effective contraception (two reliable forms) prior to initiating therapy. Patients (male and female) must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during REBETOL and for 6 months posttherapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy. (See **CONTRAINDICATIONS and WARNINGS.**)

If pregnancy does occur during treatment or during 6 months posttherapy, the patient must be advised of the teratogenic risk of REBETOL therapy to the fetus. Patients, or partners of patients, should immediately report any pregnancy that occurs during treatment or within 6 months after treatment cessation to their physician. Physicians should report such cases by calling 1-800-727-7064.

Patients receiving REBETOL Capsules should be informed of the benefits and risks associated with treatment, directed in its appropriate use, and referred to the patient **MEDICATION GUIDE**. Patients should be informed that the effect of treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus should be taken.

The most common adverse experience occurring with REBETOL Capsules is anemia, which may be severe. (See **ADVERSE REACTIONS.**) Patients should be advised that laboratory evaluations are required prior to starting therapy and periodically thereafter. (See **Laboratory Tests.**) It is advised that patients be well hydrated, especially during the initial stages of treatment.

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Laboratory Tests The following laboratory tests are recommended for all patients treated with REBETOL Capsules, prior to beginning treatment and then periodically thereafter.

- •Standard hematologic tests - including hemoglobin (pretreatment, week 2 and week 4 of therapy, and as clinically appropriate [see **WARNINGS**]), complete and differential white blood cell counts, and platelet count.
- •Blood chemistries - liver function tests and TSH.
- •Pregnancy - including monthly monitoring for women of childbearing potential.
- •ECG (See **Warnings**)

Carcinogenesis and Mutagenesis Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose). Ribavirin was non-carcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg adult). However, this dose was less than the maximum tolerated dose, and therefore the study was not adequate to fully characterize the carcinogenic potential of ribavirin.

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20-200 mg/kg (estimated human equivalent of 1.67 - 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 - 1 X the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

Impairment of Fertility Ribavirin demonstrated significant embryocidal and/or teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted.

Fertile women and partners of fertile women should not receive REBETOL unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 days, effective contraception must be utilized for 6 months posttherapy (eg, 15 half-lives of clearance for ribavirin).

REBETOL should be used with caution in fertile men. In studies in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25 - 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1 - 0.8 X the maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

Animal Toxicology Long-term studies in the mouse and rat (18 - 24 months; doses of 20 - 75 and 10 - 40 mg/kg/day, respectively {estimated human equivalent doses of 1.67 - 6.25 and 1.43 - 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1 - 0.4 X the maximum human 24-hour dose of ribavirin}) have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

Pregnancy Category X (see **CONTRAINDICATIONS)**

Ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 X the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 X the maximum recommended human 24-hour dose of ribavirin).

Treatment and Posttreatment: Potential Risk to the Fetus Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 - 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 X the maximum recommended human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

Women of childbearing potential should not receive REBETOL unless they are using effective contraception (two reliable forms) during the therapy period. In addition, effective

contraception should be utilized for 6 months posttherapy based on a multiple-dose half-life ($t_{1/2}$) of ribavirin of 12 days.
Male patients and their female partners must practice effective contraception (two reliable forms) during treatment with REBETOL and for the 6-month posttherapy period (eg, 15 half-lives for ribavirin clearance from the body).

If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment cessation, physicians should report such cases by calling 1-800-727-7064.

Nursing Mothers It is not known whether the REBETOL product is excreted in human milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to delay or discontinue REBETOL.

Geriatric Use Clinical studies of REBETOL/INTRON A or PEG-INTRON therapy did not include sufficient numbers of subjects aged 65 and over to determine if they respond differently from younger subjects.

REBETOL is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments should be made accordingly. REBETOL should not be used in patients with creatinine clearance <50 mL/min. (See WARNINGS.)

In general, REBETOL Capsules should be administered to elderly patients cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic and/or cardiac function, and of concomitant disease or other drug therapy. In clinical trials, elderly subjects had a higher frequency of anemia (67%) than did younger patients (28%). (See WARNINGS.)

Pediatric Use
Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up (see WARNINGS). As in adult patients, pediatric patients experienced other psychiatric adverse events (eg, depression, emotional lability, somnolence), anemia, and neutropenia (see WARNINGS). During a 48-week course of therapy there was a decrease in the rate of linear growth (mean percentile assignment decrease of 9%) and a decrease in the rate of weight gain (mean percentile assignment decrease of 13%). A general reversal of these trends was noted during the 24-week post-treatment period.

Drug Interactions
Didanosine: Co-administration of REBETOL Capsules or Oral Solution and didanosine is not recommended. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis,

and symptomatic hyperlactactemia/lactic acidosis have been reported in clinical trials (see **CLINICAL PHARMACOLOGY: Drug Interactions**).

Stavudine and Zidovudine: Ribavirin may antagonize the *in vitro* antiviral activity of stavudine and zidovudine against HIV. Therefore, concomitant use of ribavirin with either of these drugs should be used with caution (see **CLINICAL PHARMACOLOGY: Drug Interactions).**

ADVERSE REACTIONS

The primary toxicity of ribavirin is hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1-2 weeks of oral therapy. (See WARNINGS.) Cardiac and pulmonary events associated with anemia occurred in approximately 10% of patients. (See WARNINGS.)

REBETOL/INTRON A Combination Therapy

In clinical trials, 19% and 6% of previously untreated and relapse patients, respectively, discontinued therapy due to adverse events in the combination arms compared to 13% and 3% in the interferon arms. Selected treatment-emergent adverse events that occurred in the US studies with ≥5% incidence are provided in **TABLE 7** by treatment group. In general, the selected treatment-emergent adverse events were reported with lower incidence in the international studies as compared to the US studies with the exception of asthenia, influenza-like symptoms, nervousness, and pruritus.

Pediatric Patients

In clinical trials of 118 pediatric patients 3 to 16 years of age, 6% discontinued therapy due to adverse events. Dose modifications were required in 30% of patients, most commonly for anemia and neutropenia. In general, the adverse event profile in the pediatric population was similar to that observed in adults. Injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in pediatric patients compared to adult patients. Conversely, pediatric patients experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration, dyspnea, and pruritus compared to adult patients. Selected treatment-emergent adverse events that occurred with ≥5% incidence among all pediatric patients who received the recommended dose of REBETOL/INTRON A combination therapy are provided in Table 7.

TABLE 7. Selected Treatment-Emergent Adverse Events: Previously Untreated and Relapse Adult Patients and Previously Untreated Pediatric Patients

Percentage of Patients			
US Previously Untreated Study		US Relapse Study	Pediatric Patients
24 weeks of treatment	48 weeks of treatment	24 weeks of treatment	48 weeks of treatment

Patients Reporting Adverse Events*	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus REBETOL (N=77)	INTRON A plus Placebo (N=76)	INTRON A Plus REBETOL (n=118)
Application Site Disorders							
Injection site inflammation	13	10	12	14	6	8	14
Injection site reaction	7	9	8	9	5	3	19
Body as a Whole - General Disorders							
Headache	63	63	66	67	66	68	69
Fatigue	68	62	70	72	60	53	58
Rigors	40	32	42	39	43	37	25
Fever	37	35	41	40	32	36	61
Influenza-like symptoms	14	18	18	20	13	13	31
Asthenia	9	4	9	9	10	4	5
Chest pain	5	4	9	8	6	7	5
Central & Peripheral Nervous System Disorders							
Dizziness	17	15	23	19	26	21	20
Gastrointestinal System Disorders							
Nausea	38	35	46	33	47	33	33
Anorexia	27	16	25	19	21	14	51
Dyspepsia	14	6	16	9	16	9	<1
Vomiting	11	10	9	13	12	8	42
Musculoskeletal System Disorders							
Myalgia	61	57	64	63	61	58	32
Arthralgia	30	27	33	36	29	29	15
Musculoskeletal pain	20	26	28	32	22	28	21
Psychiatric Disorders							
Insomnia	39	27	39	30	26	25	14
Irritability	23	19	32	27	25	20	10
Depression	32	25	36	37	23	14	13
Emotional lability	7	6	11	8	12	8	16

Concentration impaired	11	14	14	14	10	12	5
Nervousness	4	2	4	4	5	4	3
Respiratory System Disorders							
Dyspnea	19	9	18	10	17	12	5
Sinusitis	9	7	10	14	12	7	<1
Skin and Appendages Disorders							
Alopecia	28	27	32	28	27	26	23
Rash	20	9	28	8	21	5	17
Pruritus	21	9	19	8	13	4	12
Special Senses, Other Disorders							
Taste perversion	7	4	8	4	6	5	<1

***** Patients reporting one or more adverse events. A patient may have reported more than one adverse event within a body system/organ class category.

In addition, the following spontaneous adverse events have been reported during the marketing surveillance of REBETOL/INTRON A therapy: hearing disorder and vertigo.

REBETOL/PEG-INTRON Combination Therapy

Overall, in clinical trials, 14% of patients receiving REBETOL in combination with PEG-INTRON, discontinued therapy compared with 13% treated with REBETOL in combination with INTRON A. The most common reasons for discontinuation of therapy were related to psychiatric, systemic (e.g. fatigue, headache), or gastrointestinal adverse events. Adverse events that occurred in clinical trial at >5% incidence are provided in **Table 8** by treatment group. Safety and effectiveness of REBETOL in combination with PEG-INTRON has not been established in pediatric patients.

Table 8. Adverse Events Occurring in > 5% of Patients

	*Percentage of Patients Reporting Adverse Events**			*Percentage of Patients Reporting Adverse Events**	
Adverse Events	**PEG-INTRON 1.5µg/kg/ REBETOL** (n=511)	**INTRON A/ REBETOL** (n=505)	Adverse Events	**PEG-INTRON 1.5µg/kg/ REBETOL** (n=511)	**INTRON A/ REBETOL** (n=505)
Application Site			**Musculoskeletal**		
Injection site Inflammation	25	18	Myalgia	56	50
Injection Site Reaction	58	36	Arthralgia	34	28
Autonomic Nervous Sys.			Musculoskeletal Pain	21	19
Mouth Dry	12	8	**Psychiatric**		
Sweating Increased	11	7	Insomnia	40	41
Flushing	4	3	Depression	31	34
Body as a Whole			Anxiety/Emotional Lability/Irritability	47	47
Fatigue/Asthenia	66	63	Concentration Impaired	17	21
Headache	62	58	Agitation	8	5
Rigors	48	41	Nervousness	6	6
Fever	46	33	**Reproductive, Female**		
Weight Decrease	29	20	Menstrual Disorder	7	6
RUQ Pain	12	6	**Resistance Mechanism**		
Chest Pain	8	7	Infection Viral	12	12
Malaise	4	6	Infection Fungal	6	1
Central/Peripheral Nervous System			**Respiratory System**		
Dizziness	21	17	Dyspnea	26	24
Endocrine			Coughing	23	16
Hypothyroidism	5	4	Pharyngitis	12	13
Gastrointestinal			Rhinitis	8	6
Nausea	43	33	Sinusitis	6	5
Anorexia	32	27	**Skin and Appendages**		
Diarrhea	22	17	Alopecia	36	32
Vomiting	14	12	Pruritus	29	28
Abdominal Pain	13	13	Rash	24	23
Dyspepsia	9	8	Skin Dry	24	23
Constipation	5	5	**Special Senses Other,**		
Hematologic Disorders			Taste Perversion	9	4

Neutropenia	26	14	**Vision Disorders**		
Anemia	12	17	Vision blurred	5	6
Leukopenia	6	5	Conjunctivitis	4	5
Thrombocytopenia	5	2			
Liver and Biliary System					
Hepatomegaly	4	4			

***Patients reporting one or more adverse events. A patient may have reported more than one adverse event within a body system/organ class category.**

Laboratory Values

REBETOL/INTRON A Combination Therapy
Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **TABLE 9**.)
Hemoglobin Hemoglobin decreases among patients receiving REBETOL therapy began at Week 1, with stabilization by Week 4. In previously untreated patients treated for 48 weeks the mean maximum decrease from baseline was 3.1 g/dL in the US study and 2.9 g/dL in the International study. In relapse patients the mean maximum decrease from baseline was 2.8 g/dL in the US study and 2.6 g/dL in the International study. Hemoglobin values returned to pretreatment levels within 4 - 8 weeks of cessation of therapy in most patients.

Bilirubin and Uric Acid Increases in both bilirubin and uric acid, associated with hemolysis, were noted in clinical trials. Most were moderate biochemical changes and were reversed within 4 weeks after treatment discontinuation. This observation occurs most frequently in patients with a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic dysfunction or clinical morbidity.

TABLE 9. Selected Hematologic Values During Treatment with REBETOL plus INTRON A: Previously Untreated and Relapse Adult Patients and Previously Untreated Pediatric Patients[17]

	Percentage of Patients						
	US Previously Untreated Study				US Relapse Study		Pediatric Patients
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=231)	INTRON A plus REBETOL (N=228)	INTRON A plus Placebo (N=225)	INTRON A plus REBETOL (N=77)	INTRON A plus Placebo (N=76)	INTRON A Plus REBETOL (n=118)
Hemoglobin (g/dL)							
9.5-10.9	24	1	32	1	21	3	24
8.0-9.4	5	0	4	0	4	0	3
6.5-7.9	0	0	0	0.4	0	0	0
<6.5	0	0	0	0	0	0	0
Leukocytes ($x10^9$/L)							
2.0-2.9	40	20	38	23	45	26	35
1.5-1.9	4	1	9	2	5	3	8
1.0-1.4	0.9	0	2	0	0	0	0
<1.0	0	0	0	0	0	0	0
Neutrophils ($x10^9$/L)							
1.0-1.49	30	32	31	44	42	34	37
0.75-0.99	14	15	14	11	16	18	15
0.5-0.74	9	9	14	7	8	4	16
<0.5	11	8	11	5	5	8	3
Platelets ($x10^9$/L)							
70-99	9	11	11	14	6	12	0.8
50-69	2	3	2	3	0	5	2
30-49	0	0.4	0	0.4	0	0	0
<30	0.9	0	1	0.9	0	0	0

Total Bilirubin (mg/dL)							
1.5 -3.0	27	13	32	13	21	7	2
3.1-6.0	0.9	0.4	2	0	3	0	0
6.1-12.0	0	0	0.4	0	0	0	0
>12.0	0	0	0	0	0	0	0

REBETOL/PEG-INTRON Combination Therapy

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **TABLE 10**.)

Hemoglobin.

REBETOL induced a decrease in hemoglobin levels in approximately two thirds of patients. Hemoglobin levels decreased to < 11g/dL in about 30% of patients. Severe anemia (<8 g/dl) occurred in < 1% of patients. Dose modification was required in 9 and 13% of patients in the PEG-INTRON/REBETOL and INTRON A/REBETOL groups.

Bilirubin and Uric Acid
In the REBETOL/PEG-INTRON combination trial 10-14% of patients developed hyperbilirubinemia and 33-38% developed hyperuricemia in association with hemolysis. Six patients developed mild to moderate gout.

Table 10: Selected Hematologic Values During Treatment with REBETOL plus PEG-INTRON

	Number (%) of Subjects				
	PEG-INTRON plus REBETOL (N=511)	INTRON A plus REBETOL (N=505)		PEG-INTRON plus REBETOL (N=511)	INTRON A plus REBETOL (N=505)
Hemoglobin (g/dL)			Platelets ($x10^9$/L)		
9.5-10.9	26	27	70-99	15	5
8.0-9.4	3	3	50-69	3	0.8
6.5-7.9	0.2	0.2	30-49	0.2	0.2
<6.5	0	0	<30	0	0
Leukocytes ($x10^9$/L)			Total Bilirubin (mg/dL)		
2.0-2.9	46	41	1.5 -3.0	10	13
1.5-1.9	24	8	3.1-6.0	0.6	0.2
1.0-1.4	5	1	6.1-12.0	0	0.2
<1.0	0	0	>12.0	0	0

Neutrophils ($x10^9$/L)			ALT (SGPT)		
1.0-1.49	33	37	2 x Baseline	0.6	0.2
0.75-0.99	25	13	2.1-5 x Baseline	3	1
0.5-0.74	18	7	5.1-10 x Baseline	0	0
<0.5	4	2	>10 x Baseline	0	0

OVERDOSAGE

There is limited experience with overdosage. Acute ingestion of up to 20 grams of REBETOL Capsules, INTRON A ingestion of up to 120 million units, and subcutaneous doses of INTRON A up to 10 times the recommended doses have been reported. Primary effects that have been observed are increased incidence and severity of the adverse events related to the therapeutic use of INTRON A and REBETOL. However, hepatic enzyme abnormalities, renal failure, hemorrhage, and myocardial infarction have been reported with administration of single subcutaneous doses of INTRON A that exceed dosing recommendations.

There is no specific antidote for INTRON A or REBETOL, and hemodialysis and peritoneal dialysis are not effective treatment of overdose of either agent.

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DOSAGE AND ADMINISTRATION (see **CLINICAL PHARMACOLOGY, Special Populations**; see **WARNINGS**)

REBETOL/INTRON A Combination Therapy

Adults

The recommended dose of REBETOL Capsules depends on the patient's body weight. The recommended dose of REBETOL is provided in **TABLE 11.**

The recommended duration of treatment for patients previously untreated with interferon is 24 to 48 weeks. The duration of treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen. (See **Description of Clinical Studies** and **ADVERSE REACTIONS.**) After 24 weeks of treatment virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV RNA below the limit of detection of the assay by 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in the previously untreated patient population.

In patients who relapse following non-pegylated interferon monotherapy, the recommended duration of treatment is 24 weeks. There are no safety and efficacy data on treatment for longer than 24 weeks in the relapse patient population.

TABLE 11. Recommended Dosing

Body weight	REBETOL Capsules
≤ 75 kg	2 x 200- mg capsules AM, 3 x 200-mg capsules PM daily p.o.
> 75 kg	3 x 200 mg capsules AM, 3 x 200 mg capsules PM daily p.o.

Pediatrics

The recommended dose of REBETOL is 15 mg/kg per day orally (divided dose AM and PM). For children weighing ≤25 kg or who cannot swallow capsules, REBETOL Oral Solution is supplied in a concentration of 40 mg/mL. For children weighing >25 kg, either the Oral Solution or 200-mg capsule may be administered Refer to Table 12 for dosing recommendations for the 200-mg capsule to achieve the recommended dose.

The recommended duration of treatment is 48 weeks for pediatric patients with genotype 1. After 24 weeks of treatment virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV RNA below the limit of detection of the assay by this time. The recommended duration of treatment for pediatric patients with genotype 2/3 is 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in pediatrics.

Table 12. Pediatric Dosing		
Body weight	REBETOL Capsules	INTRON A Injection
25-36 kg	1 x 200 mg capsule AM 1 x 200 mg capsule PM daily p.o.	3 million IU/m^2 3 times weekly s.c.
37-49 kg	1 x 200 mg capsule AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m^2 3 times weekly s.c.
50-61 kg	2 x 200 mg capsules AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m^2 3 times weekly s.c.
>61 kg	Refer to adult dosing table	Refer to adult dosing table

REBETOL may be administered without regard to food, but should be administered in a consistent manner with respect to food intake. (See **CLINICAL PHARMACOLOGY.)**

REBETOL/PEG-INTRON Combination Therapy

The recommended dose of REBETOL Capsules is 800 mg/day in 2 divided doses: two capsules (400 mg) in the morning with food and two capsules (400 mg) in the evening with food.

Dose Modifications (*TABLE 13*)

If severe adverse reactions or laboratory abnormalities develop during combination REBETOL/INTRON A therapy the dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, REBETOL/INTRON A therapy should be discontinued.

REBETOL should not be used in patients with creatinine clearance <50 mL/min. (**See WARNINGS and CLINICAL PHARMACOLOGY, Special populations.**)

REBETOL should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped. (See **WARNINGS.)**

For patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by ≥2 g/dL during any 4-week period. In addition, for these cardiac history patients, if the hemoglobin remains <12 g/dL after 4 weeks on a reduced dose, the patient should discontinue combination REBETOL/INTRON A therapy.

It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her REBETOL dose reduced to 600 mg daily (1 x 200- mg capsule AM, 2 x 200 mg capsules PM) for adults and 7.5 mg/kg per day (divided dose AM and PM) for pediatric patients. A patient whose hemoglobin level falls below 8.5 g/dL should be permanently discontinued from REBETOL therapy. (See **WARNINGS**.)

TABLE 13. Guidelines for Dose Modifications and Discontinuation for Anemia

	Dose Reduction* REBETOL – 600 mg daily adults 7.5 mg/kg daily for pediatrics	Permanent Discontinuation of REBETOL Treatment
Hemoglobin		
No Cardiac History	**<10 g/dL**	**<8.5 g/dL**
Cardiac History Patients	**≥ 2 g/dL decrease during any 4-week period during treatment**	**<12 g/dL after 4 weeks of dose reduction**

HOW SUPPLIED

REBETOL 200-mg Capsules are white, opaque capsules with REBETOL, 200 mg, and the Schering Corporation logo imprinted on the capsule shell; the capsules are packaged in a bottle containing 42 capsules (NDC 0085-1327-04), 56 capsules (NDC 0085-1351-05), 70 capsules. (NDC 0085-1385-07, and 84 capsules (NDC 0085-1194-03).

REBETOL Oral Solution 40 mg/mL is a clear, colorless to pale or light yellow bubble gum-flavored liquid and it is packaged in 4-oz. amber glass bottles (100 mL/bottle) with child-resistant closures. (NDC 0085-1318-01)

Storage Conditions

The bottle of REBETOL Capsules should be stored-at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

REBETOL Oral Solution should be stored between 2° and 8°C (36° and 46°F) or at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

Schering Corporation
Kenilworth, NJ 07033 USA

U.S. Patents 4,530,901 & 4,211,771

B-XXXXXXX Rev. 8/01

F-24819914

MEDICATION GUIDE

REBETOL (ribavirin, USP) Capsules and Oral Solution

Read this medication guide carefully before you or your child begin taking REBETOL [REB-eh-tol] Capsules or Oral Solution, and each time you refill your prescription in case new information has been included. This summary does not tell you everything about REBETOL Capsules or Oral Solution. Your health care provider is the best source of information about this medicine. After reading this medication guide, talk with your health care provider if you have any questions about REBETOL.

What is the most important information I should know about therapy with REBETOL Capsules or Oral Solution?

- **REBETOL Capsules and Oral Solution may cause birth defects or death of an unborn child. Therefore, if you are pregnant or your sexual partner is pregnant, do not take REBETOL.** If you could become pregnant, you must not become pregnant during therapy and for 6 months after you have stopped therapy. During this time you must use 2 forms of birth control, and you must have pregnancy tests that show that you are not pregnant.

Female sexual partners of male patients being treated with REBETOL must not become pregnant during treatment and for 6months after treatment has stopped. Therefore, you must use 2 forms of birth control during this time.

If pregnancy occurs, report the pregnancy to your health care provider right away. (See **"What should I avoid while taking REBETOL?")**

- After each use of Rebetol Oral Solution, wash the measuring cup or spoon to avoid accidental swallowing of the medicine.

- **REBETOL Capsules and Oral Solution can cause a dangerous drop in your red blood cell count.**
  REBETOL Capsules and Oral Solution can cause anemia, which is a decrease in the number of red blood cells. This can be dangerous, especially if you have heart or breathing problems. Tell your health care provider before taking REBETOL if you have ever had any of these problems. Your health care provider should check your red blood cell count before you start therapy and often during the first 4 weeks of therapy. Your red blood cell count may be checked more often if you have any heart or breathing problems.

- **Do not take REBETOL Capsules or Oral Solution alone to treat hepatitis C infection.**
  REBETOL Capsules should be used in combination with interferon alfa-2b (INTRON A) or in combination with peginterferon alfa-2b (PEG-INTRON) for treating chronic hepatitis C infection in adults. In children, safety and effectiveness of REBETOL Capsules or Oral Solution has only

been shown when used in combination with interferon alfa-2b (INTRON A). REBETOL Capsules and INTRON A when used together are called REBETRON Combination Therapy. Your health care provider or pharmacist should give you a copy of the REBETRON Combination Therapy or PEG-INTRON Medication Guide. They have additional important information about combination therapy not covered in this guide.

What is REBETOL (ribavirin)?

"REBETOL" is the antiviral drug ribavirin. It is used in combination with interferon alfa-2b to treat some patients with chronic hepatitis C infection. It is not known how REBETOL and interferon alfa-2b work together to fight hepatitis C infection. **(see the REBETRON Combination Therapy or PEG-INTRON Medication Guide**).

It is not known if treatment with REBETOL and interferon alfa-2b will cure hepatitis C virus infections or prevent cirrhosis, liver failure, or liver cancer that can be caused by hepatitis C virus infections. It is not known if treatment with REBETOL and interferon alfa-2b will prevent an infected person from infecting another person with the hepatitis C virus.

Who should not take REBETOL Capsules or Oral Solution?

Do not use these medicines if:

- You are a female and you are pregnant or plan to become pregnant at any time during your treatment with REBETOL or during the 6 months after your treatment has ended.
- You are a male patient with a female sexual partner who is pregnant or plans to become pregnant at any time while you are being treated with REBETOL or during the 6 months after your treatment has ended. (See **"What is the most important information I should know about therapy with REBETOL Capsules or Oral Solution?"** and "**What should I avoid while taking REBETOL Capsules or Oral Solution?")**
- You are breast-feeding. REBETOL may pass through your milk and harm your baby. Talk with your provider about whether you should stop breast-feeding.
- You are allergic to any of the ingredients in REBETOL Capsules or Oral Solution. See the ingredients listed at the end of this Medication Guide.

Tell your health care provider before starting treatment with REBETOL Capsules or Oral Solution in combination with interferon alfa-2b if you have any of the following medical conditions:

- **mental health problems, such as depression or anxiety**. REBETOL/interferon alfa-2b therapy may make them worse. Tell your health care provider if you are being treated or had treatment in the past for any mental problems, including depression, suicidal behavior, or a feeling of loss of contact with reality, such as hearing voices or seeing things that are not there (psychosis). Tell your health care provider if you take any medicines for these problems.
- **high blood pressure, heart problems, or have had a heart attack.** REBETOL Capsules and Oral Solution may worsen heart problems. Patients who have had certain heart problems should not take REBETOL Capsules or Oral Solution.
- **blood disorders,** including anemia (low red blood cell count), thalassemia (Mediterranean anemia), and sickle-cell anemia. REBETOL Capsules and Oral Solution can reduce the number of

red blood cells you have. This may make you feel dizzy or weak and could worsen any heart problems you might have.

- **kidney problems.** If your kidneys do not work properly, you may experience worse side effects from REBETOL therapy and require a lower dose.
- **liver problems** (other than hepatitis C infection)
- **organ transplant**, and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system).
- **thyroid disease**. REBETOL/interferon alfa-2b therapy may make your thyroid disease worse or harder to treat. REBETOL/interferon alfa-2b therapy may be stopped if you develop thyroid problems that cannot be controlled by medicine.
- **lung problems.** REBETOL/interferon alfa-2b Therapy can cause breathing problems or worsen breathing problems you already have.
- **alcoholism or drug abuse or addiction**
- **cancer**
- **infection with hepatitis B virus and/or human immunodeficiency virus** (the virus that causes AIDS).
- **diabetes.** REBETOL/interferon alfa-2b therapy may make your diabetes worse or harder to treat.
- **past interferon treatment for hepatitis C virus infection that did not work for you.**

For more information see the Rebetron Combination Therapy or PEG-INTRON Medication Guides.

How should I take REBETOL Capsules or Oral Solution?

Your health care provider has determined the correct dose of REBETOL Capsules or Oral Solution based on your weight. Your health care provider may lower your dose of REBETOL if you have side effects.

- It is important to follow your dosing schedule and your health care provider's instructions on how to take your medicines.
- If you take REBETOL with PEG-INTRON, take it with food.
- If you take REBETOL with INTRON A, you can take it with or without food. However, you should **take it the same way every day**.
- Take the medicine for as long as prescribed and do not take more than the recommended dose.
- If you miss a dose of REBETOL Capsules or Oral Solution, take the missed dose as soon as possible during the same day. If an entire day has gone by, check with your health care provider about what to do. Do not double the next dose.
- Tell your health care provider if you are taking or planning to take other prescription or non-prescription medicines, including vitamin and mineral supplements, and herbal medicines.
- Tell your provider before taking REBETOL Capsules or Oral Solution if you have ever had any heart or breathing problems. Your provider should check your red blood cell count before starting therapy and often during the first 4 weeks of therapy. Your red blood cell count may be checked more frequently if you have had heart or breathing problems.
- Females taking REBETOL Capsules or Oral Solution or female sexual partners of male patients taking REBETOL Capsules or Oral Solution must have a pregnancy test before treatment begins,

every month during treatment, and for 6 months after treatment ends to make sure there is no pregnancy.

What should I avoid while taking REBETOL Capsules or Oral Solution?
Avoid the following during rebetol capsule or oral solution treatment:

- **Pregnancy:** If you or your sexual partner gets pregnant during treatment with REBETOL Capsules or Oral Solution or in the 6 months after treatment ends, tell your health care provider right away. (See "**What is the most important information I should know about therapy with REBETOL Capsules or Oral Solution?**")

  Talk with your health care provider about how to avoid pregnancy. If you or your sexual partner gets pregnant while on REBETOL or during the 6 months after your treatment ends, you must report the pregnancy to your health care provider right away. Your health care provider should call Schering, the company that makes REBETOL at 1-800-727-7064. Your health care provider will be asked to give follow-up information about the pregnancy. Any information about your pregnancy that is reported about you will be confidential.

- **Breastfeeding**. The medicine may pass through your milk and harm the baby.
- **Drinking alcohol**, including beer, wine, and liquor. This may make your liver disease worse.
- **Taking other medicines**. Take only medicines prescribed or approved by your health care provider. These include prescription and non-prescription medicines and herbal supplements.

What are the most common side effects of REBETOL Capsules and Oral Solution?

The most serious possible side effects of REBETOL Capsules and Oral Solution are:

- **Harm to unborn children**. REBETOL Capsules and Oral Solution may cause birth defects or death of an unborn child. (For more details, see **"**What is the most important information I should know about REBETOL Capsules or Oral Solution?**")**
- **Anemia**. Anemia is a reduction in the number of red blood cells you have which can be dangerous, especially if you have heart or breathing problems. Tell your health care provider right away if you feel tired, have chest pain or shortness of breath. These may be signs of low red blood cell counts.

Tell your provider right away if you have any of the following symptoms. They may be signs of a serious side effect:

- **trouble breathing**
- **hives or swelling**
- **chest pain**
- **severe stomach or low back pain**
- **bloody diarrhea or bloody stools (bowel movements). These may appear black and tarry.**
- **bruising**

- **other bleeding**

The most common side effects of REBETOL Capsules and Oral Solution are:

- **feeling tired**
- **nausea and appetite loss**
- **rash and itching**
- **cough**

This summary does not include all possible side effects of REBETOL therapy. Talk to your health care provider, if you do not feel well while taking REBETOL. Your health care provider can give you more information about managing your side effects.

What should I know about hepatitis C infection?

Hepatitis C infection is a disease caused by a virus that infects the liver. This liver infection becomes a continuing (chronic) condition in most patients. Patients with chronic hepatitis C infection may develop cirrhosis, liver cancer, and liver failure. The virus is spread from one person to another by contact with the infected person's blood. You should talk to your health care provider about ways to prevent you from infecting others.

How do I store my REBETOL Capsules?

Store REBETOL Capsules at room temperature 77°F (25°C).

How do I store my REBETOL Oral Solution?

Store REBETOL Oral Solution at room temperature 77°F (25°C) or in the refrigerator 36° to 46°F (2° to 8°C).

General advice about prescription medicines
Do not use REBETOL Capsules or Oral Solution for conditions for which they were not prescribed. If you have any concern about REBETOL Capsules or Oral Solution, ask your health care provider. Your health care provider or pharmacist can give you information about REBETOL Capsules or Oral Solution that was written for health care professionals. Do not give this medicine to other people, even if they have the same condition you have.

Ingredients:

REBETOL Capsules contain ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue #2 aluminum lake.

REBETOL Oral Solution contains ribavirin and the inactive ingredients sodium citrate, citric acid, sodium benzoate, glycerin, sucrose, sorbitol, propylene glycol, and water.

THIS MEDICATION GUIDE HAS BEEN APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION.

MANUFACTURED BY:

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